DIPHTHERIA EVIDENCE TO RECOMMENDATIONS TABLE[i]

More information can be found in the review of the epidemiology of diphtheria 2000-2016[1] systematic review on immunogenicity to assess the duration of protection ⩾ 10 years after the last diphtheria booster dose and in the summary of the Strategic Advisory Group of Experts (SAGE) on Immunization.[2,3]

Question: What is the duration of continued seroprotection of diphtheria vaccination (≥10 years) conveyed by a specific schedule of diphtheria toxoid (-containing) vaccination which is comprised of at least 3 vaccine doses (primary series) and 3 booster doses until adulthood.

Population: Immunocompetent children and adults.

Intervention: Vaccination with diphtheria toxoid (-containing) vaccination.

Comparison: No vaccination, or different duration between vaccination and serological testing.

Outcome: Diphtheria serum antibody levels/ seroprevalence.

Background: Throughout history, diphtheria has been one of most feared childhood diseases globally, characterized by devastating epidemics affecting mainly children. The current WHO recommendation which dates back from 2006 states that a primary series of diphtheria-tetanus acellular/wholecell pertussis (DTwP)- or (DTaP)-(containing) vaccines should be administered in 3 doses, starting as early as 6 weeks of age, and given with a minimum interval of 4 weeks. To compensate for the loss of natural boosting, industrialized countries should add childhood boosters of diphtheria toxoid to the primary immunization series of infancy. Booster doses should be given after the completion of the primary series. Boosting at the age of 12 months, at school entry and just before leaving school are all possible options, based on the local epidemiology. In addition to childhood (and adolescent) immunizations, WHO currently recommends that people living in low-endemic or non-endemic areas may require booster injections of diphtheria toxoid at about 10-year intervals to maintain life-long protection. A review of diphtheria epidemiology[1] and a systematic review of literature[2] was conducted to assess the need for administration of decennial diphtheria toxoid booster doses in adulthood.

In April 2017, SAGE revisited this current recommendation in light of primary immunization plus 3 booster doses administered until adulthood.

[1] Review of diphtheria epidemiology http://www.who.int/immunization/sage/meetings/2017/april/1_Final_report_Clarke_april3.pdf?ua=1, accessed May 2017
[2] Systematic review of duration of protection. http://www.who.int/immunization/sage/meetings/2017/april/2_Review_Diphtheria_results_April2017_final_clean.pdf?ua=1, accessed May 2017.
[3] Summary of the April 2017 meeting of the Strategic Advisory Group of Experts on Immunization. http://www.who.int/immunization/sage/meetings/2017/april/SAGE_April_2017_Meeting_Web_summary.pdf?ua=1, accessed May 2017

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	Diphtheria is well-controlled in the majority of countries globally. Nevertheless, several large-scale outbreaks have been reported in the recent past, in particular from the South-East Asian region.	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention *Are the desirable anticipated effects large?*	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Diphtheria toxoid is one of the oldest vaccines in current use. Diphtheria vaccination has led to a drastic decline of cases since its inclusion in the Expanded Programme for Immunization (EPI) in 1974 (with diphtheria vaccine as one of the original six EPI antigens). The incidence of diphtheria decreased dramatically worldwide. During the period 1980–2000, the total number of reported diphtheria cases was reduced by >90%. The benefit of the intervention would be an overall reduction of the number of diphtheria toxoid vaccine. Benefits would entail reduced direct and indirect costs, benefits for the vaccine recipient with reduced number of health care visits and injections as well as programmatic benefits.	
	Harms of the intervention *Are the undesirable anticipated effects small?*	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	Diphtheria toxoid is one of the safest vaccines available. However, local reactions at the site of injection are common, although reported rates differ (<10 to >50%). Severe reactions are rare, and to date no anaphylactic reactions attributable to the diphtheria component have been described. With reduction of the number of doses received, the risk of adverse events would	

			decrease.	
	Balance between benefits and harms	*Favours intervention* ☒ | *Favours comparison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | *Unclear* ☐	Balancing benefits and harms of the intervention and the comparison, clearly favours the intervention.	
	What is the overall certainty of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☐ | *High* ☒ Safety of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☐ | *High* ☐	For detailed information on the certainty of evidence for the critical outcomes, please see: We are highly confident that 6 doses of diphtheria toxoid containing vaccines convey a protective immunity until at least age 39, likely longer. Concerning the safety of the intervention, we did not list a quality rating, as GARDE profiles on DTP vaccines from randomized controlled trials and observational studies are available in the following systematic review of literature. http://www.who.int/immunization/sage/meetings/2015/april/8_Safety_DTP_RCTs_obs_studies_draft.pdf?ua=1	

VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☒ *No known undesirable outcomes* ☐	No evidence available though it is assumed that in general there is no important uncertainty or variability.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *<u>Varies</u>* ☐	It is presumed that the desirable effects (reduced number of health care visits/injections) are large relative to undesirable effects (uncertainty of overall duration of protection).	
RESOURCE USE	Are the resources required small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *<u>Varies</u>* ☐	No resources needed for the intervention.	
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☒ *<u>Varies</u>* ☐	The costs of diphtheria (-containing) vaccines are already low. Non administration of decennial booster doses will further reduce indirect an direct costs and reduce the necessary resources.	

EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐	Health inequalities would be decreased without the administration of decennial booster doses, which may be affordable only in some countries.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Non- administration of decennial booster doses is presumed to be an acceptable option to key stakeholders.	
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	As no additional injections (using combination vaccines) and less health care visits are needed (without decennial booster doses), the interventions is acceptable to the target population.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐		

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub) populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	As diphtheria toxoid is almost exclusively administered in fixed combination with other vaccines, immunization programmes will need to harmonize immunization schedules between diphtheria, tetanus and, in parts, pertussis vaccination. A primary series of 3 doses of diphtheria-containing vaccine is recommended followed by 3 booster doses before adulthood. Decennial diphtheria booster doses are not recommended.				
Implementation considerations	With an increasing proportion of boys and girls attending school worldwide, immunization programmes targeting school-aged children are increasingly important. This is particularly relevant for the booster doses of diphtheria-containing vaccine.				

Monitoring and evaluation	Improved national surveillance and reporting systems, with district-level data analysis, are essential. Countries should report all available data on diphtheria cases, including utilizing data from their integrated disease surveillance and response databases and on diphtheria caused by *C. diphtheria* and *C.ulcerans* for countries with established laboratory confirmation. Epidemiological surveillance ensuring early detection of diphtheria outbreaks should be in place in all countries, and all countries should have access to laboratory facilities for reliable identification of toxigenic C. *diphtheriae*.
Research priorities	Immunity gaps may occur in older age groups due to waning immunity, but available data are insufficient to make firm recommendations. Further studies, including serosurveys, are required to generate information on the duration of protection and the need for booster doses in older age groups. Further data should be generated on transmission of cutaneous diphtheria possibly leading to respiratory diphtheria.

[i] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/